EFFECT OF THE BLOOD FUNCTION ERROR ON THE ESTIMATED KINETIC PARAMETERS WITH DYNAMIC PET

Yafang Cheng and İmam Şamil Yetik

Department of Electrical Engineering, Medical Imaging Research Center, Illinois Institute of Technology
Chicago, IL, 60616

ABSTRACT

PET is an imaging modality widely used in areas such as Oncology, Neurology, Cardiology and Neuropsychology/Cognitive neuroscience. Dynamic PET, in contrast to static PET, can identify temporal variations in the radiotracer concentration. Mathematical modeling of the tissue of interest in dynamic PET can be simplified using compartment models as a linear system where the time activity curve of a specific tissue is the convolution of the tracer concentration in the plasma and the impulse response of the tissue containing kinetic parameters. Since the arterial sampling of blood to acquire the value of the tracer concentration is invasive, blind identification to estimate both the blood input function and the kinetic parameters has recently drawn attention. Several methods have been developed for this purpose, but the effect of the estimated blood on the estimation of the kinetic parameters is not studied. In this paper, we present a mathematical model to compute the error in the kinetic parameter estimates caused by the error in estimation of the blood input function. Computer simulations show that analytical expressions we derive are sufficiently close to results obtained from optimization. Our findings are conceptually important to observe the effect of the blood function on kinetic parameter estimation, but also practically useful to evaluate various blind methods.

Index Terms— Dynamic Positron emission tomography, kinetic parameter estimation, blind methods, estimation of blood function

1. INTRODUCTION

Positron emission tomography (PET) is a functional imaging modality to observe the physiological processes in the body. To conduct a PET scan, positron-emitting radioisotopes, as a tracer, are injected into the living subject (usually into blood circulation). When positron encounters and annihilates an electron, it emits two gamma rays in reverse directions which will be sensed at two detectors at roughly the same time. Hence it is possible to locate the source along the line of response using a scanner around the subject. The data from the detector is then used to reconstruct an image of the subject [1].

Temporal variation of the tracer concentration can be obtained through dynamic imaging so that the physiological function of the subject can be tracked more accurately. Therefore, dynamic imaging is a useful tool for various clinical and research applications [2]–[6].

A two-compartment model is used to simplify the kinetic model of the tracer molecule of interest. In this model, the input $C_p(t)$ is the tracer concentration in the plasma, and the output is the time activity curve (TAC). Let $f(t)$ denote the TAC of a specific tissue, then the relation between $f(t)$ and the impulse response of the ith tissue $h^{(i)}(t)$ containing the kinetic parameters is

$$f(t) = h(t) * C_p(t). \tag{1}$$

For two-compartment tissue modeling, $h(t)$ is [1]

$$h^{(i)}(t) = k_I^{(i)} \cdot e^{-t \cdot k_O^{(i)}}, \tag{2}$$

where k_I is the washin rate constant (uptake) and k_O is the washout rate constant.

Estimation of the kinetic parameters k_I and k_O based on $f(t)$ requires that the blood function $C_p(t)$ is known. The classical method of arterial sampling to obtain the blood function has several disadvantages: it requires well-trained medical personnel and poses a health risk to the subject. Therefore, blind methods are developed to estimate the kinetic parameters of the tissue response without knowing input function. In such methods, the input function is estimated along with the kinetic parameters of the tissue impulse model of interest. Several studies have been done in the field, such as maximum likelihood, cross relation methods, and several others, see [8]– [11] and references therein.

For noisy TAC measurements we can use the following model

$$f^{(i)}(t_n) = h^{(i)}(t_n) * C_p(t_n) + \varepsilon^{(i)}(t_n), \tag{3}$$

which can be written as

$$\vec{f}^{(i)} = H^{(i)}\overrightarrow{C_p} + \vec{\varepsilon}^{(i)}, \tag{4}$$

where $H^{(i)}$ is the convolution matrix of the impulse response of the tissue for region i, C_p denotes the vector of the blood function, and $\vec{\varepsilon}^{(i)}$ is the noise vector. Stacking different regions of interest together, we can write the equations in the following form

$$\overrightarrow{TACs} = H\overrightarrow{C_p} + \vec{\varepsilon}. \tag{5}$$

We can estimate the kinetic parameters and the blood function by minimizing the following cost function

$$R = \|\overrightarrow{TACs} - \hat{H}\overrightarrow{\hat{C}_p}\|^2. \tag{6}$$

Several methods for blind kinetic parameter estimation has been proposed, but no study has shown the effect of errors in the estimated blood on the estimation of kinetic parameters. In this paper, we develop a mathematical model that can compute this effect. Our results can be used to calculate the error in the kinetic parameter estimates steming from the errors in the blood function that is used. Our derivations is on the implicit function theorem previously used for static PET [12] and the Runge-Kutta methods [7].

Although, these errors in the parameters can be found performing a separate optimization for each of the error combinations in the blood that we want to study, this is a very time consuming method, considering that the optimization procedure is iterative. This is especially important when we are interested in pixel by pixel kinetic

parameter estimation, and/or when the space of the erronous blood functions we want to analyze is large. Based on the results of this paper, the optimization need to be performed only once, and the error propogation can be calculated very fast based on this single optimization.

2. DERIVATION OF THE ERROR PROPOGATION

In this section, we explain how we can calculate the errors in the kinetic parameters due to the error in the blood function. The estimates of the kinetic parameters $\hat{k_I}$, $\hat{k_O}$ are

$$[\hat{k_I}, \hat{k_O}] = \arg \min_{\hat{k_I}, \hat{k_O}} R([\hat{k_I}, \hat{k_O}], \hat{C_p}). \quad (7)$$

Our goal is to obtain the errors in the kinetic parameters Δk_I and Δk_O stemming from the error in the blood function ΔC_p. The first step in this calculation is to calculate the derivatives of the implicit estimator with respect to the elements of $C_p(t)$. This calculation can be performed by using the chain rule and implicit function theorem [12].

For a solution k_I, k_O that minimizes the cost function the partial derivatives of cost function with respect to the kinetic parameters is zero

$$\begin{aligned} 0 &= \frac{\partial}{\partial k_I} R([\hat{k_I}, \hat{k_O}], \hat{C_p})\Big|_{k_I=\hat{k_I}}, \\ 0 &= \frac{\partial}{\partial k_O} R([\hat{k_I}, \hat{k_O}], \hat{C_p})\Big|_{k_O=\hat{k_O}}. \end{aligned} \quad (8)$$

Let us define an implicit function

$$[\hat{k_I}, \hat{k_O}] = g(\hat{C_p}) = [g_1(\hat{C_p}), g_2(\hat{C_p})]'. \quad (9)$$

that maps the $\hat{C_p}$ into an estimate$[\hat{k_I}, \hat{k_O}]$. We can rewrite (8) as

$$\begin{aligned} 0 &= \frac{\partial}{\partial k_I} R(g(\hat{C_p}), \hat{C_p}), \\ 0 &= \frac{\partial}{\partial k_O} R(g(\hat{C_p}), \hat{C_p}). \end{aligned} \quad (10)$$

By applying the chain rule to this equation, we can differentiate the above two equations with respect to $\hat{C_p}$ and obtain

$$\begin{aligned} 0 &= \frac{\partial^2}{\partial k_I^2} R(g(\hat{C_p}), \hat{C_p}) \frac{\partial}{\partial \hat{C_p}} g_1(\hat{C_p}) \\ &+ \frac{\partial^2}{\partial k_I \partial k_O} R(g(\hat{C_p}), \hat{C_p}) \frac{\partial}{\partial \hat{C_p}} g_2(\hat{C_p}) \\ &+ \frac{\partial^2}{\partial k_I \partial \hat{C_p}} R(g(\hat{C_p}), \hat{C_p}), \\ 0 &= \frac{\partial^2}{\partial k_O \partial k_I} R(g(\hat{C_p}), \hat{C_p}) \frac{\partial}{\partial \hat{C_p}} g_1(\hat{C_p}) \\ &+ \frac{\partial^2}{\partial k_O^2} R(g(\hat{C_p}), \hat{C_p}) \frac{\partial}{\partial \hat{C_p}} g_2(\hat{C_p}) \\ &+ \frac{\partial^2}{\partial k_O \partial \hat{C_p}} R(g(\hat{C_p}), \hat{C_p}). \end{aligned} \quad (11)$$

In matrix form, where $\hat{C_{p_n}}$ is the nth sample of the estimated input blood function.

$$\begin{bmatrix} -\frac{\partial^2}{\partial k_I \partial \hat{C_{p_n}}} R \\ -\frac{\partial^2}{\partial k_O \partial \hat{C_{p_n}}} R \end{bmatrix} = \begin{bmatrix} \frac{\partial^2}{\partial k_I^2} R & \frac{\partial^2}{\partial k_I \partial k_O} R \\ \frac{\partial^2}{\partial k_O \partial k_I} R & \frac{\partial^2}{\partial k_O^2} R \end{bmatrix} \begin{bmatrix} \frac{\partial g_1(\hat{C_p})}{\partial \hat{C_{p_n}}} \\ \frac{\partial g_2(\hat{C_p})}{\partial \hat{C_{p_n}}} \end{bmatrix}. \quad (12)$$

Then a simple matrix inversion provides

$$\begin{bmatrix} \frac{\partial g_1(\hat{C_p})}{\partial \hat{C_{p_n}}} \\ \frac{\partial g_2(\hat{C_p})}{\partial \hat{C_{p_n}}} \end{bmatrix} = \begin{bmatrix} \frac{\partial^2}{\partial k_I^2} R & \frac{\partial^2}{\partial k_I \partial k_O} R \\ \frac{\partial^2}{\partial k_O \partial k_I} R & \frac{\partial^2}{\partial k_O^2} R \end{bmatrix}^{-1} \begin{bmatrix} -\frac{\partial^2}{\partial k_I \partial \hat{C_{p_n}}} R \\ -\frac{\partial^2}{\partial k_O \partial \hat{C_{p_n}}} R \end{bmatrix}, \quad (13)$$

The elements of the matrix and the vector on the right hand side can be calculated based on the cost function

$$\begin{aligned} \frac{\partial^2 R}{\partial k_I^2} &= 2\overrightarrow{C_p}' \left(\frac{\partial H}{\partial k_I}\right)' \frac{\partial H}{\partial k_I} \overrightarrow{C_p} \\ \frac{\partial^2 R}{\partial k_O \partial k_I} &= -2\overrightarrow{C_p}' \left(\frac{\partial^2 H}{\partial k_I \partial k_O}\right)' \overrightarrow{TACs} \\ &+ 2\overrightarrow{C_p}' \left(\frac{\partial^2 H}{\partial k_I \partial k_O}\right)' H\overrightarrow{C_p} + 2\overrightarrow{C_p}' \left(\frac{\partial H}{\partial k_I}\right)' \frac{\partial H}{\partial k_O} \overrightarrow{C_p} \\ \frac{\partial^2 R}{\partial k_O^2} &= -2\overrightarrow{C_p}' \left(\frac{\partial^2 H}{\partial k_O^2}\right)' \overrightarrow{TACs} + 2\overrightarrow{C_p}' \left(\frac{\partial^2 H}{\partial k_O^2}\right)' H\overrightarrow{C_p} \\ &+ 2\overrightarrow{C_p}' \left(\frac{\partial H}{\partial k_O}\right)' \frac{\partial H}{\partial k_O} \overrightarrow{C_p} \\ \frac{\partial^2 R}{\partial k_I \partial \hat{C_{p_n}}} &= -2[0 \dots 1_{n_{th}} \dots 0] \left(\frac{\partial H}{\partial k_I}\right)' \overrightarrow{TACs} \\ &+ 2[0 \dots 1_{n_{th}} \dots 0] \left(\frac{\partial H}{\partial k_I}\right)' H\overrightarrow{C_p} \\ &+ 2\overrightarrow{C_p}' \left(\frac{\partial H}{\partial k_I}\right)' H[0 \dots 1_{n_{th}} \dots 0]' \\ \frac{\partial^2 R}{\partial k_O \partial \hat{C_{p_n}}} &= -2[0 \dots 1_{n_{th}} \dots 0] \left(\frac{\partial H}{\partial k_O}\right)' \overrightarrow{TACs} \\ &+ 2[0 \dots 1_{n_{th}} \dots 0] \left(\frac{\partial H}{\partial k_O}\right)' H\overrightarrow{C_p} \\ &+ 2\overrightarrow{C_p}' \left(\frac{\partial H}{\partial k_O}\right)' H[0 \dots 1_{n_{th}} \dots 0]' \end{aligned} \quad (14)$$

where " $'$ " denotes the transpose. The terms $\frac{\partial H}{\partial k_I}$, $\frac{\partial H}{\partial k_O}$, $\frac{\partial^2}{\partial k_I \partial k_O} H$, $\frac{\partial^2}{\partial k_O^2} H$ can be calculated using the compartment model:

$$\begin{aligned} \frac{\partial H}{\partial k_I} &= \text{Convmatrix}[e^{-k_O t}], \\ \frac{\partial H}{\partial k_O} &= \text{Convmatrix}[-k_I t e^{-k_O t}], \\ \frac{\partial^2}{\partial k_I \partial k_O} H &= \text{Convmatrix}[-t e^{-k_O t}], \\ \frac{\partial^2}{\partial k_O^2} H &= \text{Convmatrix}[k_I t^2 e^{-k_O t}], \end{aligned} \quad (15)$$

where "Convmatrix" denotes an operation converting a vector to its corresponding convolution matrix.

Because of the presence of k_I and k_O in the terms $\frac{\partial k_I}{\partial \hat{C_{p_n}}}$ and $\frac{\partial k_O}{\partial \hat{C_{p_n}}}$, we cannot simply integrate $\frac{\partial k_I}{\partial \hat{C_{p_n}}} \Delta \hat{C_{p_n}}$ and $\frac{\partial k_O}{\partial \hat{C_{p_n}}} \Delta \hat{C_{p_n}}$ to obtain the errors in the kinetic parameter estimates. However, we can calculate $\frac{\partial k_I}{\partial \hat{C_{p_n}}}$ and $\frac{\partial k_O}{\partial \hat{C_{p_n}}}$ at a fixed point of $\hat{C_{p_n}}$, and a sequential procedure can be applied to calculate a new value of k_I and k_O, and we can use them to evaluate $\frac{\partial k_I}{\partial \hat{C_{p_n}}}$ and $\frac{\partial k_O}{\partial \hat{C_{p_n}}}$ at the next C_p value until the complete range of ΔC_p is covered. This procedure can be performed by methods such as Runge-Kutta methods, predictor-corrector method and Richardson extrapolation. In this paper, we

modify regular Runge-Kutta methods [7] for ODE to adapt to partial differential equations. By far the most common approximation is the fourth-order Runge-Kutta approximation.

$$\begin{aligned} k_{1,i} &= hf_i(C_{p_n}, k_I, k_O) \\ k_{2,i} &= hf_i(C_{p_n} + \frac{h}{2}, k_I + \frac{k_{1,1}}{2}, k_O + \frac{k_{1,2}}{2}) \\ k_{3,i} &= hf_i(C_{p_n} + \frac{h}{2}, k_I + \frac{k_{2,1}}{2}, k_O + \frac{k_{2,2}}{2}) \\ k_{4,i} &= hf_i(C_{p_n} + h, k_I + k_{3,1}, k_O + k_{3,2}) \\ y_i(C_{p_n} + h) &= y_i(C_{p_n}) + \frac{k_{1,i}}{6} + \frac{k_{2,i}}{3} + \frac{k_{3,i}}{3} + \frac{k_{4,i}}{6}, \quad (16) \end{aligned}$$

where $i = 1, 2$ for k_I and k_O, h is the small step size we define according to the demand on accuracy and speed, and

$$\begin{aligned} f_1 &= \frac{\begin{bmatrix} -\frac{\partial^2}{\partial k_I \partial \hat{C_{p_n}}} R & \frac{\partial^2}{\partial k_I \partial k_O} R \\ -\frac{\partial^2}{\partial k_O \partial \hat{C_{p_n}}} R & \frac{\partial^2}{\partial k_O^2} R \end{bmatrix}}{\begin{vmatrix} \frac{\partial^2}{\partial k_I^2} R & \frac{\partial^2}{\partial k_I \partial k_O} R \\ \frac{\partial^2}{\partial k_O \partial k_I} R & \frac{\partial^2}{\partial k_O^2} R \end{vmatrix}}, \\ f_2 &= \frac{\begin{bmatrix} \frac{\partial^2}{\partial k_I^2} R & -\frac{\partial^2}{\partial k_I \partial \hat{C_{p_n}}} R \\ \frac{\partial^2}{\partial k_O \partial k_I} R & -\frac{\partial^2}{\partial k_O \partial \hat{C_{p_n}}} R \end{bmatrix}}{\begin{vmatrix} \frac{\partial^2}{\partial k_I^2} R & \frac{\partial^2}{\partial k_I \partial k_O} R \\ \frac{\partial^2}{\partial k_O \partial k_I} R & \frac{\partial^2}{\partial k_O^2} R \end{vmatrix}}. \quad (17) \end{aligned}$$

Let us define

$$\begin{aligned} k_{I_{\text{start}}} &= y_1(C_{p_n}), \\ k_{O_{\text{start}}} &= y_2(C_{p_n}), \\ k_{I_{\text{after one step}}} &= y_1(C_{p_n} + h), \\ k_{O_{\text{after one step}}} &= y_2(C_{p_n} + h). \quad (18) \end{aligned}$$

In multi-dimension, we perform the calculations N times for every C_{p_n} for a single step

$$\begin{aligned} k_{I_{\text{after one step}}} &= k_{I_{\text{current}}} + \sum_{n=1}^{N} \frac{\partial k_I}{\partial \hat{C_{p_n}}} \Delta \hat{C_{p_n}}, \\ k_{O_{\text{after one step}}} &= k_{O_{\text{current}}} + \sum_{n=1}^{N} \frac{\partial k_O}{\partial \hat{C_{p_n}}} \Delta \hat{C_{p_n}}. \quad (19) \end{aligned}$$

This completes the calculation of the errors in k_I and k_O stemming from the error in estimation of C_{p_n} with error bound being $O(h^5)$.

3. COMPUTER SIMULATIONS

We apply the proposed mathematical model to simulated data with t = [0.25, 0.5, 0.75, 1.0, 1.25, 1.5, 1.75, 2.0, 2.5, 3.0, 3.5, 7.0, 10.0, 15.0, 20.0, 30.0, 60.0, 90.0, 120.0]. and $k_I = 1.0$, $k_O = 0.8$.

We have performed two sets of experiments. For these three experiments, we set an error margin for C_{p_n} and compare the propogated errors in k_I and k_O using the derived expressions and optimization. We use CGM for optimization.

First, we test the mathematical model in one dimension and assume that one of the 19 samples of C_{p_n} has an error up to 30% defined as $\frac{C_{p_n}(error) - C_{p_n}(true)}{C_{p_n}(true)}$. Figure 1 shows a comparison of

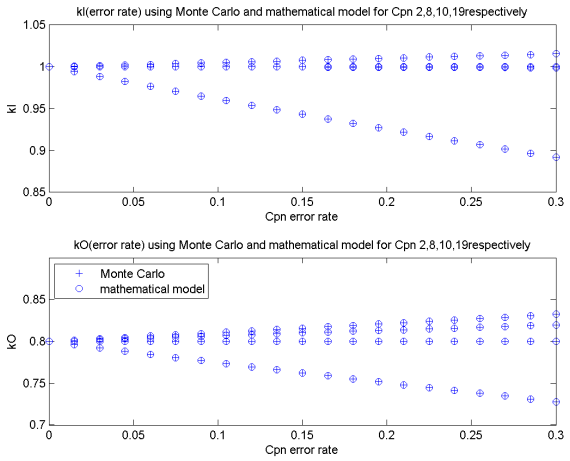

Fig. 1. Comparison between the estimated k_I and k_O using the derived expressions and optimization for a range of errenous blood functions. A single sample out of 19 samples of C_{p_n} has an error. The results are given for four random samples.

the results from the derived expressions and optimization for four random samples of C_p. We observe that the derived expressions provide very accurate approximations of the the errors in k_I and k_O.

For several of the blind methods, the error in the blood function is usually not confined in a single sample. Therefore in our second experiment, we use a blood function with multiple errenous samples. The blood function is divided into two parts: (i) the initial peak and (i) the tail part. Based on this grouping three cases of errors are considered: Case I, all samples; Case II, initial peak with samples 1 to 13; Case III, tail part with samples 14 to 19. All errenous sample have the same error rate ranging from 0 to 30%.

Figure 2 shows that the results from the derived expressions is very close to ones from numerical optimization. When all 19 samples have the same error rate from 0 to 30%, we can see that the error in k_O is negligibly small while k_I changes from 1.0 to 0.7692 with numerical optimization and 0.7688 with the derived expressions. This can be explained with (3) where scaling in the blood function would not affect k_O but inversely scale k_I. For case II, we observe that k_I deviates from the true value more than k_O, indicating that the error in the initial peak affects the estimation of kinetic parameter k_I more than k_O. For case III, we observe a reversed effect; the error in the tail part affects the estimation of kinetic parameter k_O more than k_I.

These simulation results show that the derived expressions provide a very accurate approximation of the errors in the kinetic parameters, and several useful observations related to the effect of the blood function on the kinetic parameter estimates can be made.

4. SUMMARY

In this paper, we have derived mathematical expressions that quantify how errors in the blood estimate propogate into errors in the kinetic parameter estimates. Computer simulations show that the proposed mathematical model can yield accurate estimates of the errors in k_I and k_O. Results can easily be generalized to more complicated compartment models.

The developed method can quantify the errors in the kinetic parameters for different error combinations in the blood function, with-

out having to perform optimization for each of the error cases to be analyzed. This would be computationally prohibitive especially for pixel by pixel kinetic parameter estimation, and large ranges of blood error to be analyzed. Future work includes generalization to estimation based on the sinogram instead of reconstructed TAC's, and application to real PET data.

5. REFERENCES

[1] M. N. Wernick, J. N. Aarsvold (Eds.), "Emission Tomography: The Fundamentals of PET and SPECT," Elsevier, 2004.

[2] M. E. Phelps, S. C. Huang, E. J. Hoffman, C. Selin, L. Sokoloff, and D. E. Kuhl, "Tomographic measurement of local cerebral glucose metabolic rate in humans with (f-18)2-fluoro-2-deoxy-d-glucose: Validation of method," *Ann. Neurol.,* vol. 6, pp. 371–388, 1979.

[3] A. A. Lammertsma and S. P. Hume, "Simplified reference tissue model for PET receptor studies," *Neuroimage*, vol. 4, pp. 153–158, 1996.

[4] H. Watabe, R. E. Carson, and H. Iida, "The reference tissue model: Three compartments for the reference region," *Neuroimage*, vol. 6, no. 4, pp. S12–S12, 2000.

[5] J. Tseng, L. K. Dunnwald, E. K. Schubert, J. M. Link, S. Minoshima, M. Muzi, and D. A. Mankoff, "F(18)-FDG kinetics in locally advanced breast cancer: correlation with tumor blood flow and changes in response to neoadjuvant chemotherapy," *Journal of Nuclear Medicine,* vol. 45, pp. 1829–1837, 2004.

[6] S. Chen, C. Ho, D. Feng, and Z. Chi, "Tracer kinetic modeling of C(11)-Acetate applied in the liver with positron emission tomography," *IEEE Trans. Med. Imag.,* vol. 23, pp. 426–432, 2004.

[7] N. Gershenfeld, "The Nature of Mathematical Modeling," Cambridge, 1999.

[8] D. Y. Riabkov, and Edward V. R. Di Bella, "Estimation of kinetic parameters without input functions: analysis of three methods for multichannel blind identification," *IEEE Trans. Biomed. Eng.,* vol. 49, pp. 1318–1327, 2002.

[9] M. I. Gürelli, and C L. Nikias, "EVAM: An eigenvector-based algorithm for multichannel blind deconvolution of input colored signals," *IEEE Trans. Signal Processing,* vol. 43, pp. 134–149, 1995.

[10] D. Feng, K. -P. Wong, C. -M. Wu and W. C. Siu, "A technique for extracting physiological parameters and the required input function simultaneously from PET image measurements: Theory and simulation study," *IEEE Trans. Inform. Technol. Biomed.,* vol. 1, pp. 243–254, 1997.

[11] K. -P. Wong, D. Feng, S. R. Meikle, and M. J. Fulham, "Simultaneous Estimation of Physiological Parameters and the Input Function In vivo PET Data," *IEEE Trans. Inf. Tech. Biomed.,* vol. 5, pp. 67–76, 2001.

[12] J. A. Fessler, "Mean and variance of implicitly defined biased estimators (such as penalized maximum likelihood): applications to tomography," *IEEE Trans. Imag. Proc.,* vol. 5, pp. 493–506, 1996.

[13] L. Kaufman, "Maximum likelihood, least squares, and penalized least squares for PET," *IEEE Trans. Med. Imag.,* vol. 12, pp. 200–214, 1993.

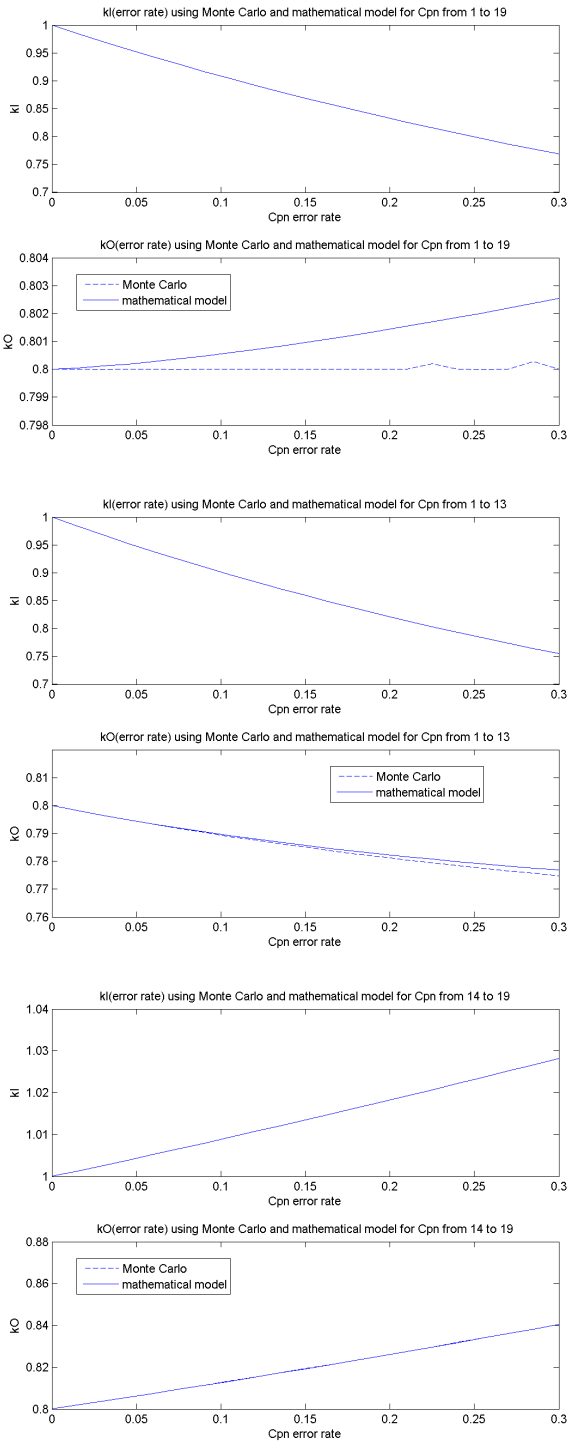

Fig. 2. Comparison between the estimated k_I and k_O using the derived expressions and optimization for a range of errenous blood functions. Top two figures show results when all samples of the blood is errenous, middle two when the initial peak is errenous, and the bottom two when the tail part is errenous.